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Promise of Tomorrow

The topics discussed in this conference represent great scientific opportunity that we will exploit in the future. The objectives of the research programs at NIEHS have been to understand how chemicals interact with living material, cell metabolism, function, and structure. If these mechanisms are understood, it is easier to make judgments about potential health effects and to suggest ways to ameliorate these effects. As Manny Farber emphasized (*1*), "We must understand the process."

This conference shows how the new biology dealing with cell growth and differentiation, regulation (intercellular communications, etc.) is being applied to specific organ systems: CNS, reproduction and development, genetic toxicology, and carcinogenesis. Much of the new biology is common to all cells and it is hoped that as we achieve greater understanding, we will be able to understand the role of chemicals in the etiology of many specific disease processes.

Although we are aware of many specific risk factors, the etiology of most chronic diseases remains unknown. Advances in basic science should permit us to determine better the role that chemicals play in these common diseases. Environmental factors have some role in many diseases, even those commonly thought of a genetic disease. If you think about it, environment has a major role in such straightforward genetic diseases as phenylketonuria (PKU). It is really the susceptibility to PKU that is inherited; the disease is due to toxicity of the excessive phenylalanine that is not metabolized. A child who is homozygous for PKU (that is, one who is deficient in phenylalanine hydroxylase and thus unable to hydroxylate phenylalanine) is normal *in utero* because the environment provided by the mother is a safe environment; after birth, that child still has the disease but only shows the mental retardation when exposed to an uncontrolled environment containing phenylalanine that cannot be metabolized by the normal pathways. If it is possible to remove phenylalanine from the diet (alter the environment), the child is normal. This may be a rather extreme view of the role of environment in disease and not what is ordinarily though of, but I want to make the point that most disease is, indeed, the result of some interaction between the environment and the constitution of the individual.

To carry the relationship between genetics and environment one step further to the realm of a common quasi genetic/environmental disease, diabetes mellitus, there are two types of diabetes, insulin-dependent and noninsulin-dependent diabetes. For insulin-dependent diabetes mellitus (IDDM), the defect is related to two abnormal genes: one is the IDDM gene; the second is one of the HLA family. Interestingly, in children with both genes, only about one-third develop the IDDM disease. Thus, the presence of the clinical disease probably is determined by an environmental factor.

And then there are a number of important chronic diseases that truly have no known etiology, like atherosclerosis. Many environmental factors have been implicated in the pathogenesis of this disorder and it may, in fact, be multifactorial. The more we learn about the cellular events that are altered in a disease, the more likely we are to pinpoint its etiology. For instance, there is increasing evidence that atheromatous plaques, a major cause of arterial disease, may be benign tumors that can contain oncogenelike materials. The tumors are monoclonal and presumably result from a carcinogen insult. These benign tumors may be influenced by environmental factors such as cholesterol, perhaps a promoter.

Cancer, of course, is probably the most frightening disease in the present world (although AIDS may be the most emotional at this particular point in time). Nevertheless, there are several approaches being pursued to treat [as elegantly presented by Dr. Waldmann (*2*)] and to prevent or control cancer. One of our roles is prevention: to study factors, particularly toxic chemicals in the environment, that may contribute to the etiology of cancer. To date, one of our major contributions continues to be to identify many chemicals having carcinogenic potential and to develop new and better research approaches on how this can be done.

Two major problems in linking a chemical to a particular cancer in a person have been, first, the long latent period between exposure to a carcinogenic chemical and the appearance of clinical cancer; and, second, that everyone is exposed to many carcinogens all the time. However, as we have heard in this conference today, new knowledge about the carcinogenic processes and the role of activated oncogenes may provide another tool we need to finally be able to link a carcinogen to the tumor in humans. Norton Nelson (*3*) and other presented the concept of the continuum from exposure to endpoint, i.e., exposure, dose, internal dose, preclinical effect, and on to frank clinical disease. Another fascinating aspect is the relation between oncogenes and chemical effects on cells and signal transduction. Some oncogenes regulate the production of proteins that are involved in cell communication, growth factors, and/or kinases.

A major group of disease touched on in these papers (4) relates to effects of toxic chemicals on the nervous system. For instance, Alzheimer's and related diseases seem to be increasing in our aging population and are of growing importance. At present there are some clues linking environmental factors with Alzheimer's and Parkinson's diseases. If we can find ways of linking subclinical neuronal damage to chemicals, using both laboratory and epidemiologic methods, we may have some basis for prevention in the future.

These are only a few examples selected to highlight new areas of promise for future research. There are other exciting techniques that must be considered. One is the use of magnetic resonance in the study of *in vivo* cell and tissue metabolism and its application in imaging. Tumors 1 mm or less in diameter can be visualized in living rats. Tomorrow's scientific advances can only be achieved by the established links between basic science, toxicology, and clinical medicine, and this meeting has demonstrated the strength and vigor of these links.

This bodes well for the future of environmental health research.

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